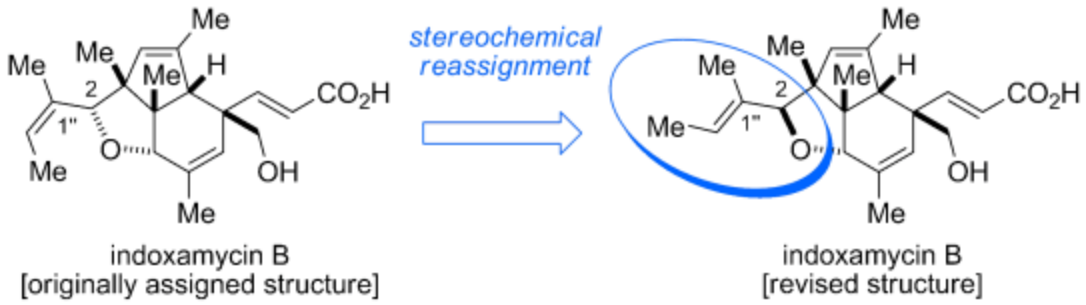
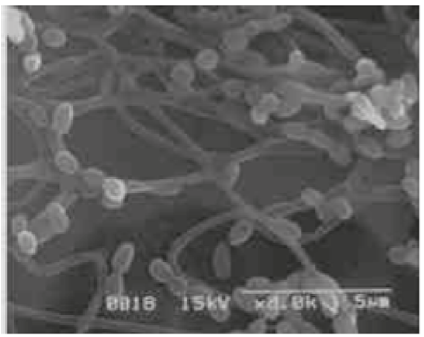
Total Synthesis and Stereochemical Reassignment of (±)-Indoxamycin B

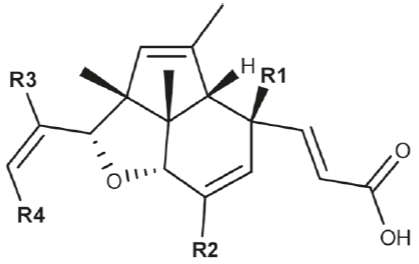
Jeker, O. F.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3474 – 3477



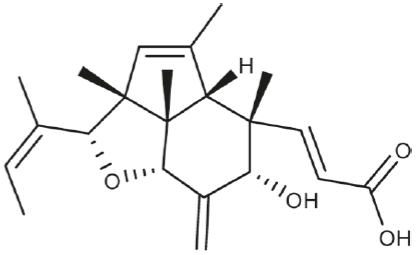
Current Literature
Jie Xu
06.09.12

Isolation





Indoxamycin A: **R1** = CH_3, **R2** = CH_3, **R3** =CH_3, **R4** =CH_3
Indoxamycin B: **R1** = CH_2OH, **R2** = CH_3, **R3** = CH_3, **R4** =CH_3
Indoxamycin C: **R1** = CH_3, **R2** = CH_2OH, **R3** = CH_3, **R4** =CH_3
Indoxamycin D: **R1** = CH_3, **R2** = CH_3, **R3** = CH_2OH, **R4** = CH_3
Indoxamycin E: **R1** = CH_3, **R2** = CH_3, **R3** =CH_3, **R4** = CH_2OH

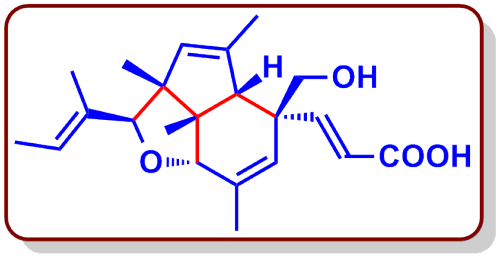


Indoxamycin F

- ***Isolated from saline cultures of marine-derived actinomycetes***
- ***Structure assigned by MS and NMR (^1H, ^{13}C, HMBC, NOSEY) and chemical methods (Mosher Ester Analysis)***
- ***Indoxamycins A and F have been shown to display growth inhibition against HT-29 tumor cell lines (IC_{50}= 0.59 μm and 0.31 μm, respectively).***

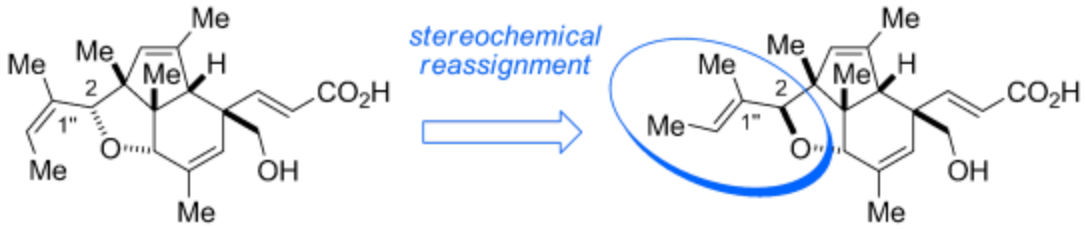
Sato, S.; Iwata, F.; Mukai, T.; Yamada, S.; Takeo, J.; Abe, A.; Kawahara, H. *J. Org. Chem.* **2009**, *74*, 5502 – 5509.
Sato, S.; Iwata, F.; Yamada, S.; Takeo, J.; Abe, A.; Kawahara, H. (Nippon Suisan Kaisha, Ltd.), WO 113725, **2010**.

Structure



Indoxamycin B

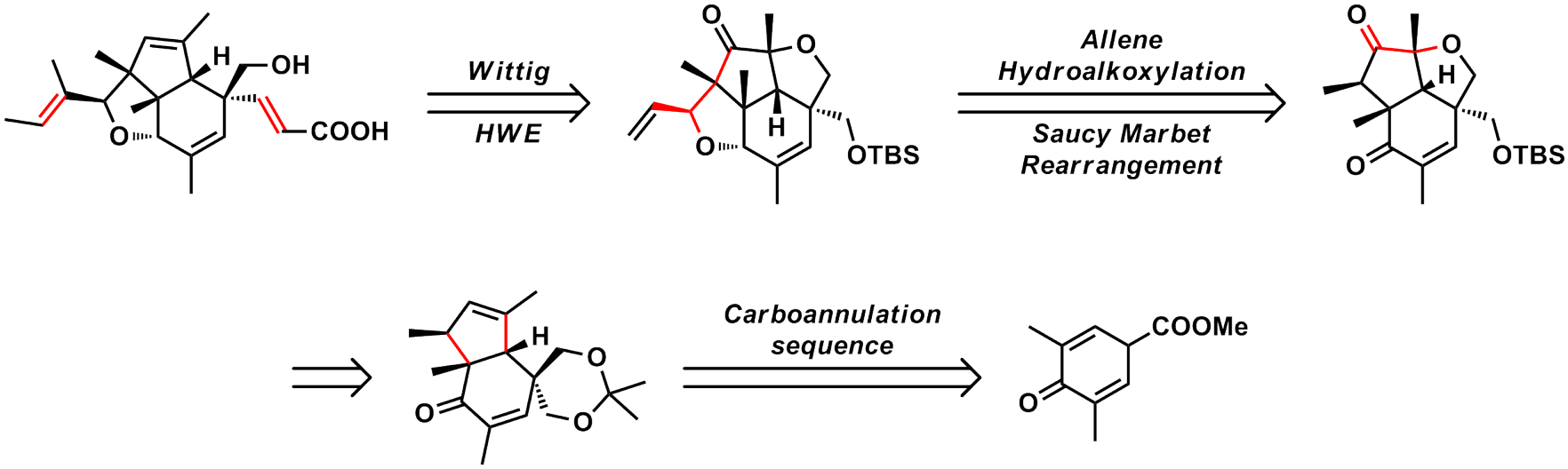
- *5,5,6-Tricyclic carbon skeleton with six contiguous asymmetric centers*
- *Three quaternary stereo centers*
- *Tri-substituted alkene side chain*
- *α,β-unsaturated carboxylic acid side chain*



indoxamycin B
[originally assigned structure]

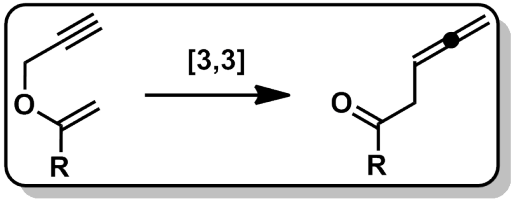
indoxamycin B
[revised structure]

Retrosynthetic Analysis

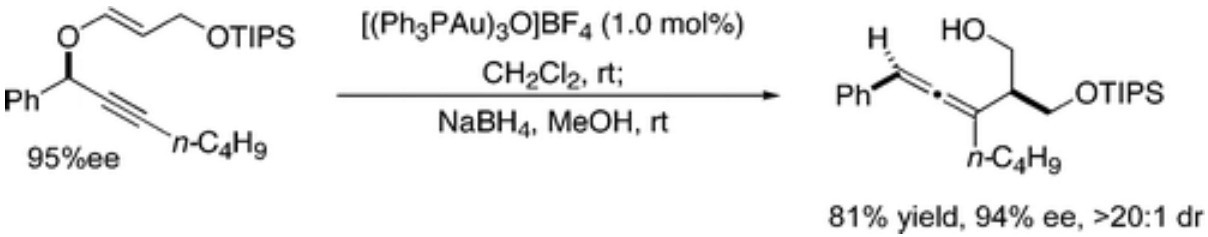


- ***Saucy-Marbet Rearrangement (Propargyl Claisen)***
- ***Allene Hydroalkoxylation***
- ***Oxidative Carboannulation***

Saucy-Marbet Rearrangement



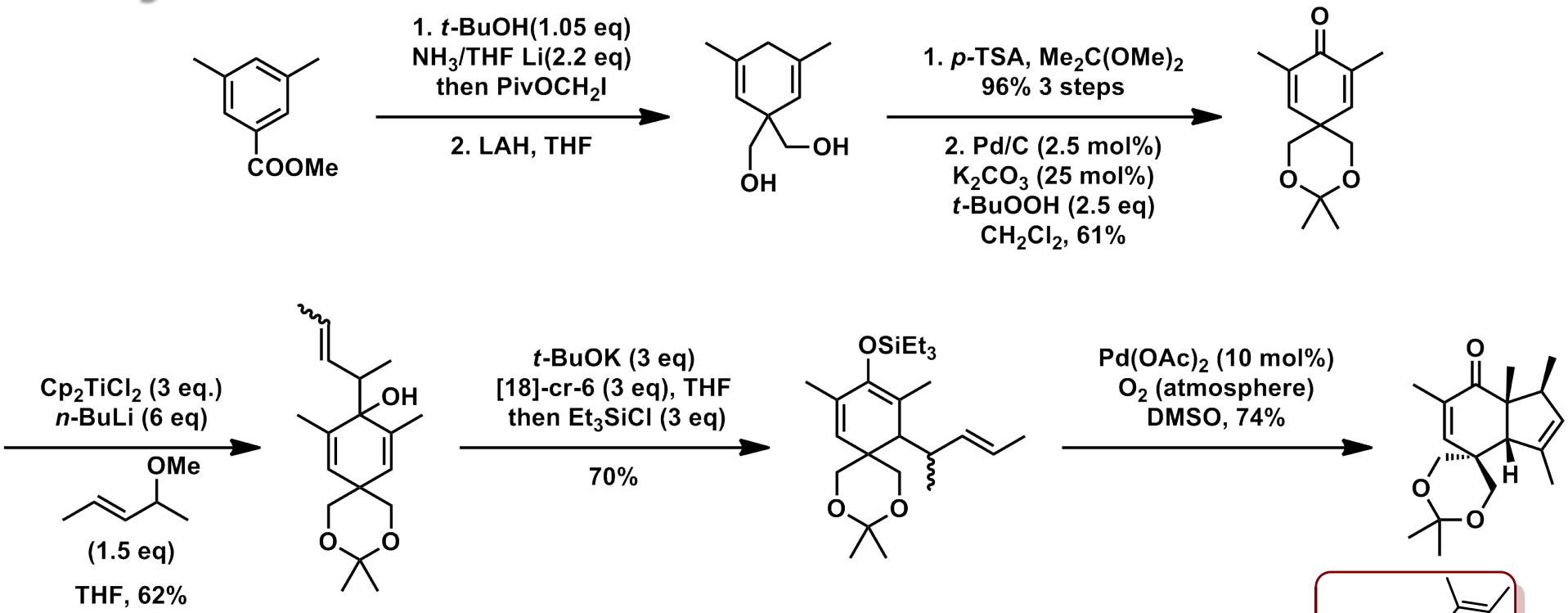
propargyl vinyl ether -> β-keto allene

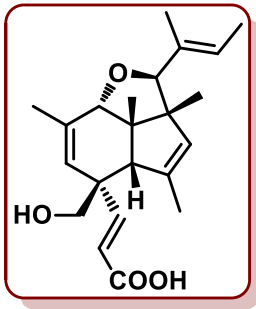


Gold catalyzed reaction
Stereo-specific

Saucy, G.; Marbet, R. *Helv. Chim. Acta.* **1967**, *50*, 1158 – 1167.
Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978 – 15979.

Synthesis

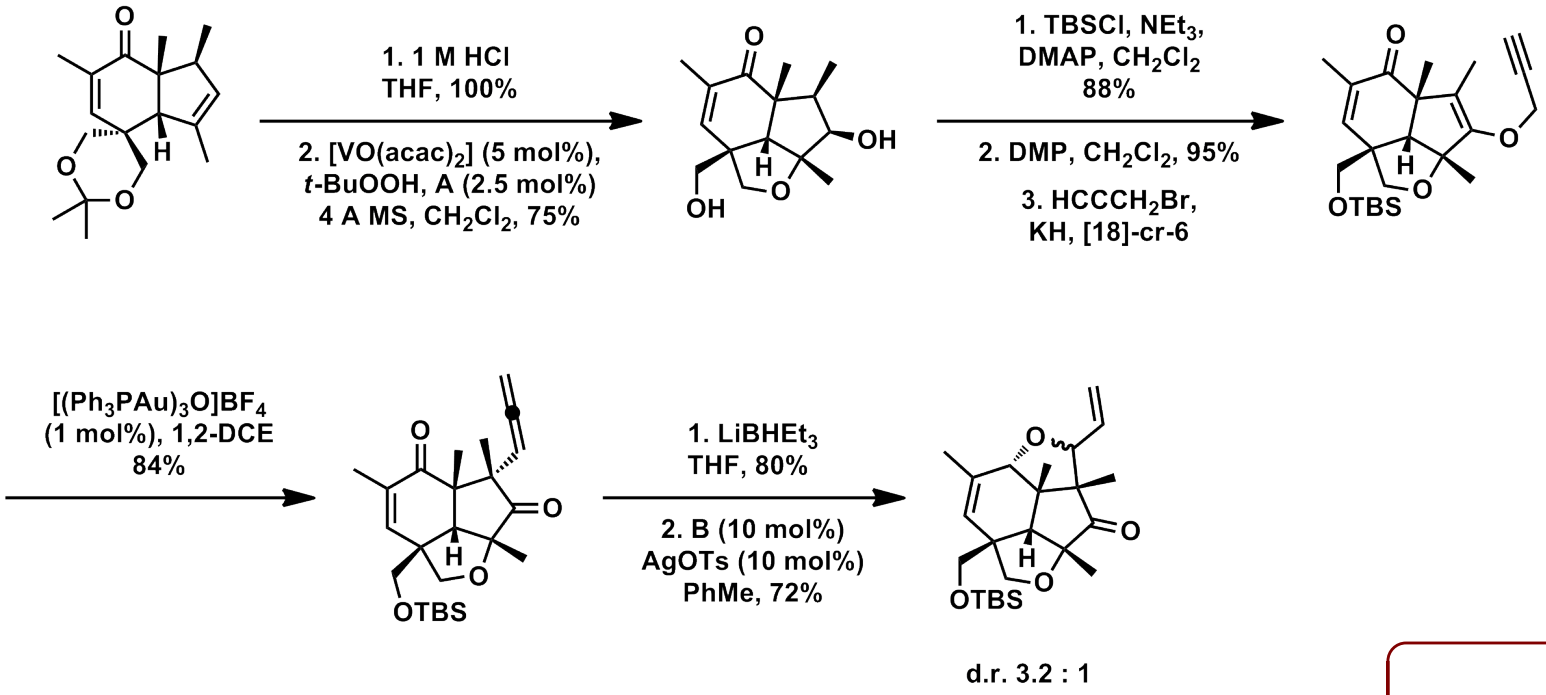


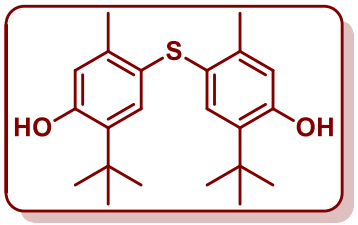


Indoxamycin B

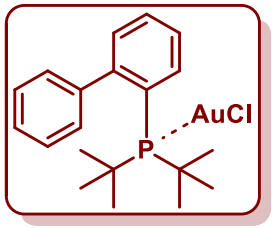
- *Reluctant to undergo conjugate addition –> anionic oxy-Cope*
- *Saguesa type oxidative carboannulation*

Au(I) Catalyzed Reaction

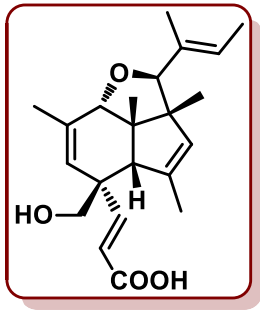




- ***A: 4,4'-thiobis(2-tert-butyl-5-methylphenol)***

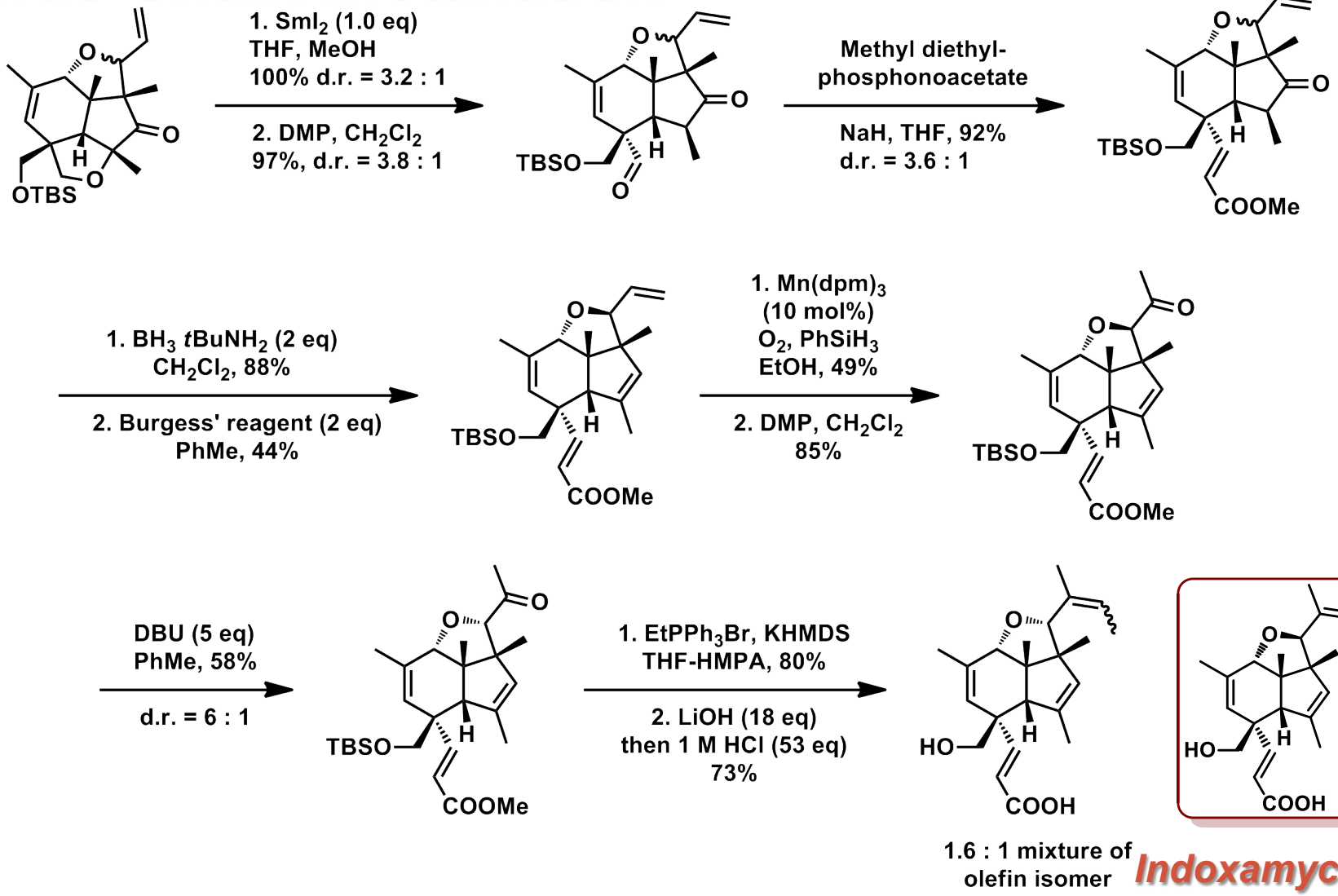


- ***B: chloro[2-(di-tert-butylphosphino) biphenyl]gold(I)***



Indoxamycin B

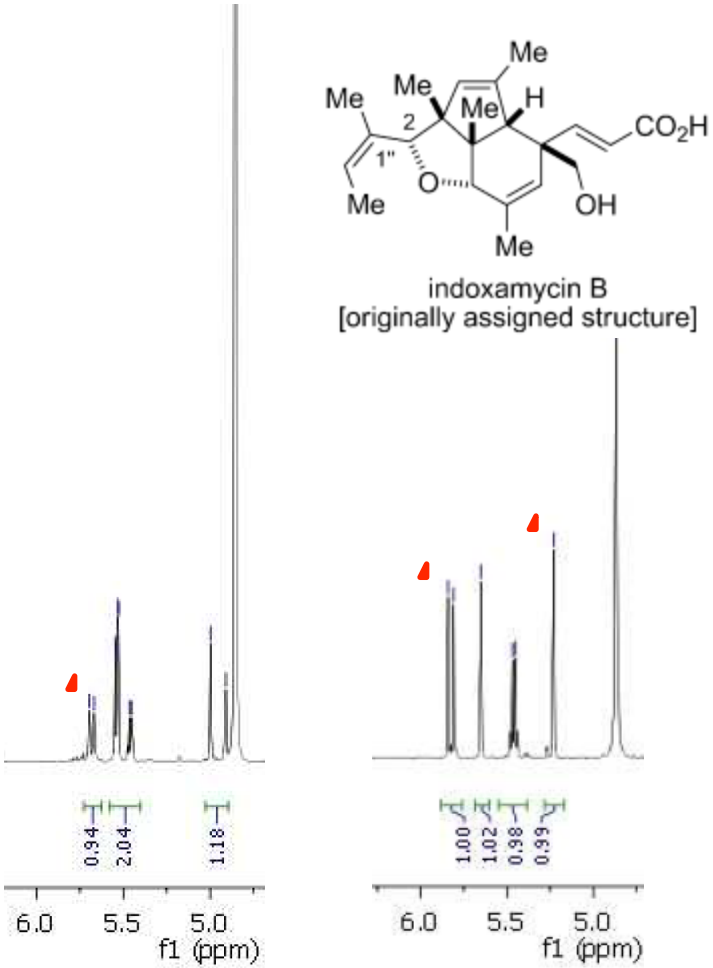
Side Chain Installation



1.6 : 1 mixture of olefin isomer

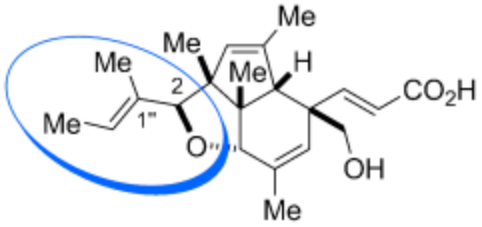
Indoxamycin B

Spectrum Conflict



indoxamycin B
[originally assigned structure]

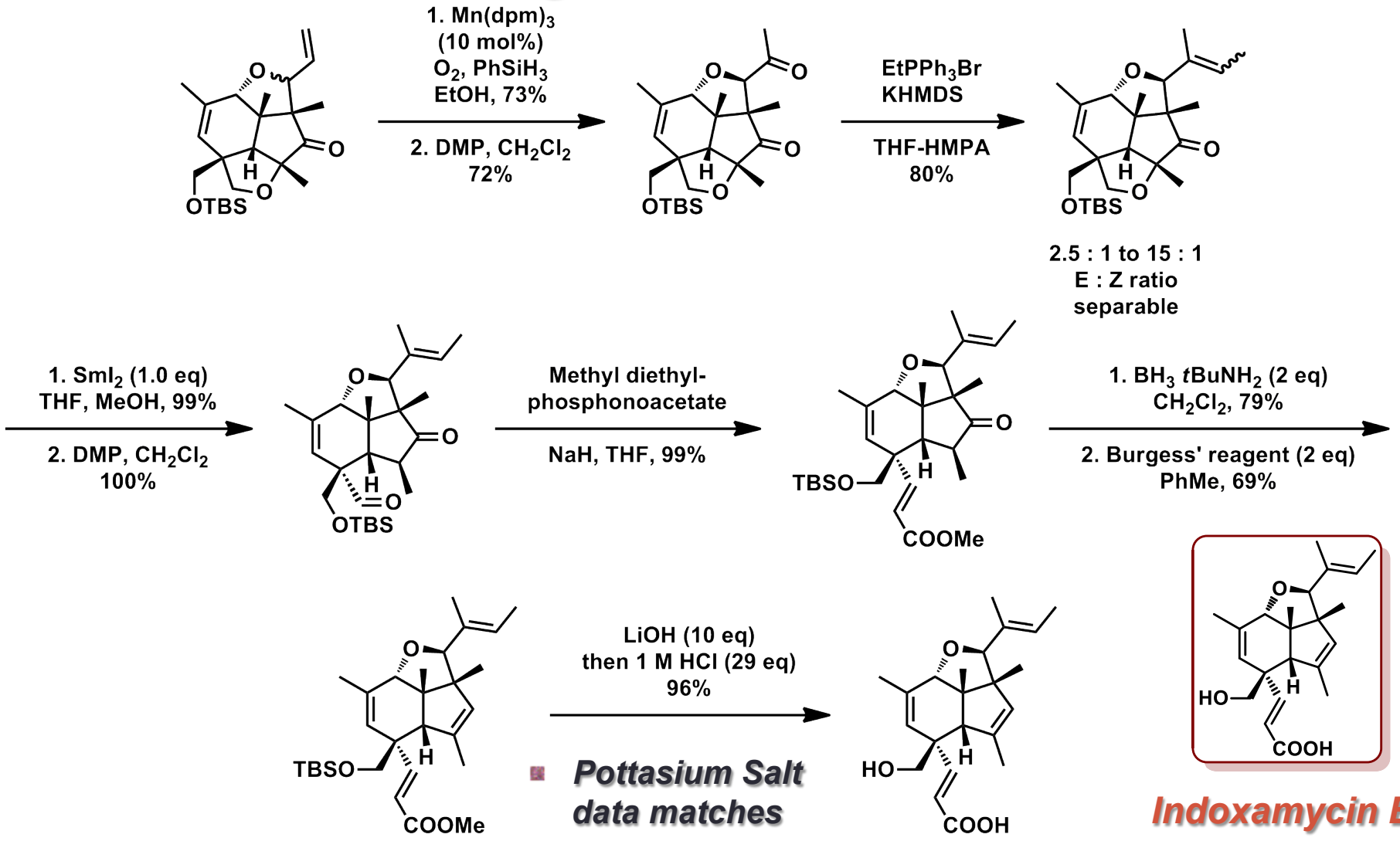
stereochemical reassignment



indoxamycin B
[revised structure]

- ***Neither isomers match the natural product***
- ***Inconstant on ^{1}H ^{13}C***

Structure Reassignment



- ***Pottasium Salt data matches***

Indoxamycin B

Summary

- *The first synthesis of (±)-Indoxamycin B and their family members (24 steps 1% overall yield)*
- *Sigma tropic rearrangement*
- *Various metal used (Li, Pd, Ti, V, Au, Sm, Mn)*
- *Structure reassignment*